Bedaquiline

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Multidrug-Resistant Tuberculosis (MDR TB)

- Resistant to Rifampin and Isoniazid
- More than 650,000 cases emerge globally every year
- Development of drug resistance attributed to: poor adherence to treatment, inadequate clinical management, drug malabsorption, unstable drug supply

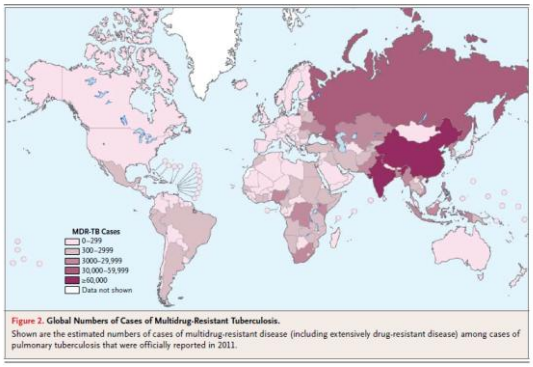
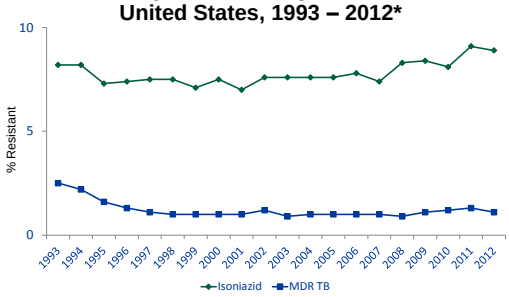


Figure 2. Global Numbers of Cases of Multidrug-Resistant Tuberculosis.
Shown are the estimated numbers of cases of multidrug-resistant disease (including extensively drug-resistant disease) among cases of pulmonary tuberculosis that were officially reported in 2011.

Primary Anti-TB Drug Resistance, United States, 1993 – 2012*



*Updated as of June 10, 2013.
Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin

Primary MDR TB in U.S.-born vs. Foreign-born Persons United States, 1993 – 2012*

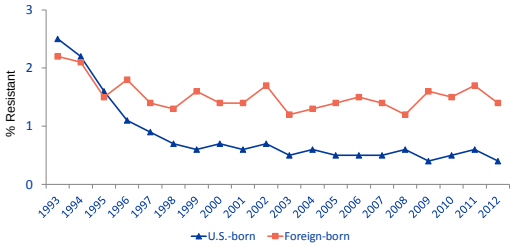


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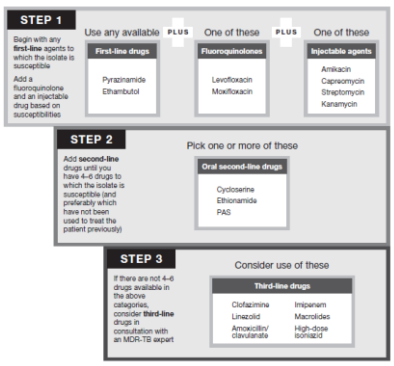
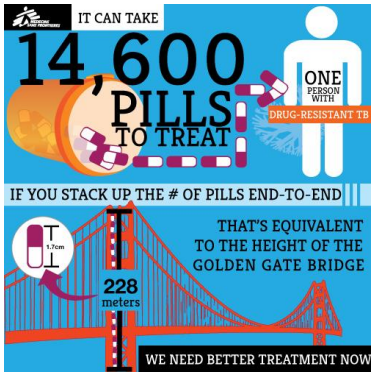
FIGURE 1.
Building a Treatment Regimen for MDR-TB

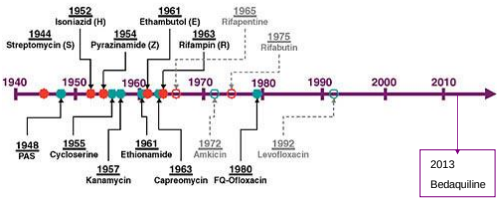


MDR-TB Prognosis

- Intensive phase: 6-8 months
- Continuation phase: 18-24 months after culture conversion
- Success rates of treatment: 52-77%
- Mortality rate: 10%



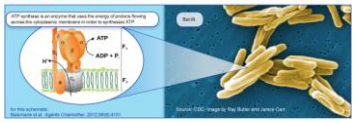
First-line TB drugs (drug-sensitive TB)



Second-line TB drugs (drug-resistant TB)

Bedaquiline (Sirturo)

- Diarylquinolone class
- Inhibits bacterial adenosine triphosphate (ATP) synthase
- This enzyme is essential for generation of energy in *Mycobacterium tuberculosis*
- Active against replicating and nonreplicating bacilli



Bedaquiline (Sirturo)

- Unique mechanism means that there is no cross-resistance with other drugs in current use
- First new class of anti-tuberculous agent since 1971

TABLE 2. Summary of three bedaquiline efficacy and safety studies

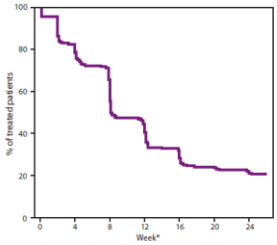
Study (Stage)	Design	Intervention and control	No. in each arm bdq/ placebo	Outcome measured	Key result	Deficiency	Population
C208 (Stage 1)	Double-blind, randomized, placebo-controlled superiority trial	BR[†] for 18–24 months +/- bdq for 8 weeks	23/24	Primary: median time to SCC* Secondary: SCC rate at weeks 8 and 24	Bdq with BR was superior to BR alone in time to SCC (hazard ratio: 11.7). Greater SCC rate noted for bdq with BR at week 8 (p = 0.004), but not at week 24.	Surrogate marker for clinical benefit; small sample size	New onset MDR TB; HIV with CD4<300 cells/mm^3 and those on ARV excluded
C208 (Stage 2)	Double-blind, randomized, placebo-controlled superiority trial	BR for 18–24 months +/- bdq for 24 weeks	80/81	Primary: median time to SCC[‡] Secondary: SCC rate at weeks 24 and 72	Bdq with BR was superior to BR alone in time to SCC (hazard ratio: 2.15). Greater SCC rate noted for bdq with BR at week 24 (p = 0.014) but not at week 72.	Surrogate marker for clinical benefit; small sample size	New onset MDR TB; HIV with CD4<300 cells/mm^3 and those on ARV excluded
C209	Noncomparative, single-arm, open-label trial	BR + bedaquiline	294	Primary:median time to SCC	Time to SCC was 57 days.	Surrogate marker for clinical benefit; observational study	Previously treated pre-XDR and XDR TB; HIV with CD4<250 cells/mm^3 excluded

Source: Adapted from Food and Drug Administration clinical pharmacology review [9].
Abbreviations: ARV = antiretroviral treatment; Bdq = bedaquiline; BR = background regimen; MDR TB = multidrug-resistant tuberculosis; XDR TB = extensively drug-resistant TB; CD4 = T-helper cell count; SCC = smear culture conversion; 95% CI = 95% confidence interval.
* Two consecutive cultures from sputum samples that were negative for *Mycobacterium tuberculosis*.
† Background regimen (ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone).

• Primary outcome measured: time to sputum culture conversion (two consecutive cultures)

•Conversion: 77.6 % vs. 57.6%

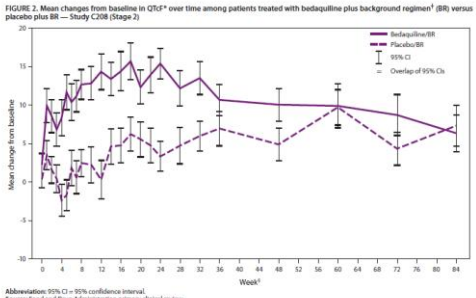
FIGURE 1. Time to sputum culture conversion (SCC) in patients treated with bedaquiline who failed previous therapy for drug-resistant pulmonary tuberculosis



Source: Adapted from Food and Drug Administration clinical pharmacology review (9).
* Time to SCC (two consecutive cultures from sputum samples that were negative for *Mycobacterium tuberculosis*) in weeks.

*Mean time to sputum culture conversion: 57 days

FIGURE 2. Mean changes from baseline in QTcF* over time among patients treated with bedaquiline plus background regimen† (BR) versus placebo plus BR — Study C208 (Stage 2)



Abbreviation: 95% CI = 95% confidence interval.
Source: Food and Drug Administration primary clinical review.
* The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death. The QT interval is dependent on the heart rate and may be corrected by calculation to improve the detection of patients at increased risk of ventricular arrhythmia. One of several calculation correction formulas focuses on the QT interval divided by cube-root of RR (QTcF), where RR is the interval from the onset of one QRS complex (the graphical deflections seen on an electrocardiogram [ECG] that correspond to the depolarization of the right and left ventricle with each heart beat) to the onset of the next QRS complex, measured in milliseconds.
† Ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone.
§ Time to smear culture conversion (two consecutive cultures from sputum samples that were negative for *Mycobacterium tuberculosis*) in weeks.

•No episodes of Torsades de Pointes occurred

TABLE 5. Mortality in bedaquiline Phase II safety studies*

		No. of deaths			
		Bedaquiline arm		Control arm	
Study (Stage)	Design	No.	(%)	No.	(%)
C202	Randomized, open-label, dose-ranging early bactericidal study using INH or RIF in control arm	2/45	(4.4)	0	0
C208 (Stage 1)	Double-blind, randomized, placebo-controlled superiority trial	2/23	(8.7)	2/124	(8.3)
C208 (Stage 2)	Double-blind, randomized, placebo-controlled superiority trial	10/79	(12.6)	4/81	(4.9)
C209	Noncomparative, single-arm, open-label trial	16/233	(6.9)	No control arm	No control arm

Source: Adapted from Food and Drug Administration clinical pharmacology review (9).
Abbreviations: INH = isoniazid; RIF = rifampin.
* Patients in the mortality analysis were followed for up to 6 months from the last recorded visit, as specified in the study safety procedures.

•Total of 36 deaths reported→30 in bedaquiline group, 6 in placebo group

•Mortality: 11.4 vs 2.5%

•No relationship between bedaquiline serum levels or QTcF>500 ms and survival outcome

December 28 2012: FDA Grants Accelerated Approval for SIRTURO™ (bedaquiline) as Part of Combination Therapy to Treat Adults with Pulmonary Multi-Drug Resistant Tuberculosis

"*Multi-drug resistant tuberculosis poses a serious health threat throughout the world, and Sirturo provides much-needed treatment for patients who have don't have other therapeutic options available. However, because the drug also carries some significant risks, doctors should make sure they use it appropriately and only in patients who don't have **other** **treatment options**.*"

-Edward Cox, M.D., M.P.H, director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research

WARNINGS:

- **An increased risk of death was seen in the SIRTURO™ (bedaquiline) treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO™ when an effective treatment regimen cannot otherwise be provided.**
- **QT prolongation can occur with SIRTURO™. Use with drugs that prolong the QT interval may cause additive QT prolongation.**

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 62 / No. 9
October 25, 2013

Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis

Indications

1. Part of combination therapy in adults (> age 18) with pulmonary multi-drug resistant tuberculosis (MDR-TB) for 24 weeks
2. Reserve for use when an effective treatment regimen cannot otherwise be provided

Other considerations:

- May be used on a case-by-case basis in:
  1. Children
  2. HIV-infected persons
  3. Persons with extrapulmonary MDR-TB
  4. Patients with comorbid conditions on concomitant medications when an effective treatment regimen cannot otherwise be provided

**effectiveness and safety of bedaquiline has not been adequately treated in these populations*

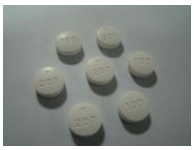
Other considerations:

- Bedaquiline may be used on a case-by-case basis for durations longer than 24 weeks when an effective treatment regimen cannot be provided otherwise

**It has not been studied past 24 weeks*

Dosing and Duration

- First two weeks: 400 mg by mouth daily
- Followed by: 200 mg by mouth three times weekly
- Treatment duration: 24 weeks



How to take

•Take with food (standard meal: 22 g fat, 558 calories)
•Swallow whole with water

Table 1: Select ADRs From a Phase 2b Study (24 weeks of SIRTURO™ exposure) That Occurred More Frequently Than Placebo During Treatment With SIRTURO™

ADRs	SIRTURO™ Treatment Group N=79 n (%)	Placebo Treatment Group N=81 n (%)
Nausea	30 (38.0)	26 (32.1)
Arthralgia	26 (32.9)	18 (22.2)
Headache	22 (27.8)	10 (12.3)
Transaminases increased*	7 (8.9)	1 (1.2)
Blood amylase increased	2 (2.5)	1 (1.2)
Hemoptysis†	14 (17.7)	9 (11.1)
Chest Pain†	9 (11.4)	6 (7.4)
Anorexia†	7 (8.9)	3 (3.7)
Rash†	6 (7.6)	3 (3.7)

* Terms represented by "transaminases increased" included transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased, and hepatic function abnormal.
† Reported adverse events with a greater incidence in the SIRTURO™ treatment group but which were not identified as ADRs.

No additional unique ADRs were identified from another Phase 2B uncontrolled study of SIRTURO™.

http://www.sirturo.com/sites/default/files/pdf/SIRTURO-product-guide.pdf

Hepatotoxicity

- Monitor AST, ALT, bilirubin, alkaline phosphatase monthly and more often if symptoms
- Avoid alcohol and other hepatotoxic drugs
- Can be administered to patients with moderate hepatic impairment (Child-Pugh A or B) but not severe hepatic impairment (Child-Pugh C)

Cardiac Toxicity (1)

- Baseline EKG should be obtained and repeated at least 2, 12 and 24 weeks after starting treatment
- Serum potassium, calcium and magnesium should be obtained at baseline and when clinically indicated

Cardiac Toxicity (2)

- Concurrent use of other drugs known to cause QTcF prolongation may increase risk of cardiotoxicity
- Weekly EKG indicated in the following:
  1. Patient on other QTcF prolonging drugs (fluoroquinolones, macrolides, clofazimine)
  2. History of torsades de pointes, congenital long QT syndrome, hypothyroidism and bradyarrythmias, or uncompensated heart failure
  3. They have serum calcium, magnesium or potassium levels below the lower limits of normal

Cardiac Toxicity (3)

- Discontinuation of bedaquiline and all other QTcF-prolonging drugs should be considered if the patient develops:

  1. Clinically significant ventricular arrhythmia or

  2. a QTcF of >500 ms
- Follow-up EKGs should be monitored to confirm QTcF returns to baseline

Drug Interactions

- Bedaquline is metabolized by the Cytochrome 3A4 system in the liver:

  -avoid medications that induce this system (i.e. rifampin)

  -avoid medications that inhibit this system (i.e. ketoconazole, Kaletra)
- No clinical data on using this drug in HIV patients who are receiving antiretrovirals

Half-life

- Extremely long terminal half-life: 4-5 months
- Acquired resistance may occur when bedaquiline is the sole effective anti-TB drug in the circulation
- Prescribers need to discontinue bedaquiline 4-5 months prior to discontinuation of other drugs

Cost

- Bedaquline 100 mg (188): $36000

Virginia Guidelines

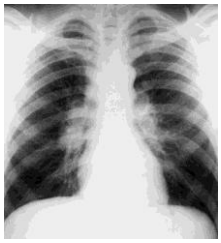
- The drug is only available through one pharmacy in the US. Every state, territory, etc. had to provide two names to CDC as those who could authorize the drug for use in their state. No one can take a prescription to a pharmacy and obtain the drug if this works as it is supposed to. Debbie Staley and Jane Moore are the names provided to the CDC as those who can administratively release this drug for use in VA.
- All cases will need to be reviewed by TB Consultants before approval is granted. Given the cost and potential toxicity, we will likely need internal approval from Dr. Trump, the state epidemiologist before proceeding.
- Obviously, absolute, in-person DOT will be required for this drug. Because of the Black Box warnings, a decision has been made that the DOT must be performed by a PHN, not an ORW, at least initially until we have more experience with this drug.

Case 1

- 28 yo HIV-negative Indian woman with no prior history of TB treatment or contacts
- Class B with positive TST, IGRA and negative CXR prior to arrival
- Presents to health department for evaluation 3 months after arrival
- She has a cough and fever

Case 1

- 3 AFB sputums obtained and are negative
- Started on 4-drug therapy



Case 1

- Mtb confirmed on culture
- First-line drug susceptibility testing returns three weeks later and shows:

  -resistance to rifampin, isoniazid, ethambutol
- Started on: pyrazinamide, Moxifloxacin, amikacin, PAS, cycloserine and azithromycin

Case 1

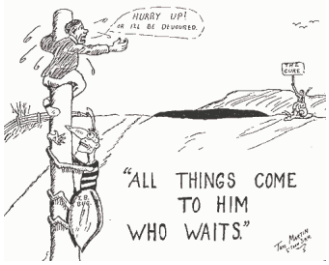
- At week 5, drug susceptibility testing showed resistance to fluoroquinolones and the following injectable agents: streptomycin, amikacin, capreomycin, kanamycin
- Therefore, moxifloxacin and amikacin were discontinued→linezolid, meropenem and augmentin were added
- At week 10, PAS susceptibility confirmed

Case 1

- Due to limited therapeutic options, application made for bedaquiline through compassionate use program
- Patient started bedaquiline at week 14
- Sputum cultures were negative starting from week 9 throughout treatment

Case 1

- EKGs were done daily in the beginning of therapy due to use of bedaquiline and azithromycin
- LFTS were monitored regularly
- Week 22: linezolid stopped due to nausea and a painful, progressive peripheral neuropathy
- Week 70: complained of vertigo, tinnitus
- Eventually completed two years of therapy



Resources

- Provisional CDC Bedaquline Guidelines: http://www.cdc.gov/mmwr/pdf/rr/rr6209.pdf
- http://www.sirturo.com/